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10/525,119	10/14/2005	Frank-Gerhard Boss	01-2114	5586

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EXAMINER	
ZAREK, PAUL E	
ART UNIT	**PAPER NUMBER**
4161	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,119	BOSS ET AL.	
	Examiner	Art Unit	
	PAUL ZAREK	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *4,5,8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02/18/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/18/2005, 07/30/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-9 are currently pending. This is the first Office Action on the merits of the claim(s).

Election/Restrictions

2. Applicant's election without traverse of Group I, the mental process, "cognitive processes," and the PDE9A inhibitor, "6-(cyclohexylmethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one," in the reply filed on 07/30/2008 is acknowledged.

3. Claims 1-3, 6, and 7 read on the elected species. Claims 4, 5, 8, and 9 are withdrawn as being drawn to a non-elected invention.

Priority

4. Applicant's claim for the benefit of a prior-filed international application, PCT/EP03/08880 (filed on 08/11/2003) under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The effective filing date of the instant application is 08/11/2003

5. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany (Application # 102 38 722.2) on 08/23/2002. It is noted, however, that applicant has not filed a certified copy of the German application as required by 35 U.S.C. 119(b).

Specification

6. The attempt to incorporate subject matter into this application by reference to http://depts.washington.edu/pde/Nomenclature.html (pg 1, line 28) is ineffective because it is improper to incorporate essential or nonessential subject matter into a patent application by reference tot he contents of the site to which it is directed (MPEP § 608.01(p)) .

7. The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims , 2, 3, and 6-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating impairments of perception, concentration, cognitive processes, learning, and/or memory, with PDE9A inhibitors, does not reasonably provide enablement for a method of preventing impairments of perception, concentration, cognitive processes, learning, and/or memory with PDE9A inhibitors.

10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

11. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (MPEP § 2164.01(a))

a. *The breadth of the claim*: Claims 1, 2, 3, and 6-7 are drawn to a method of treatment or prophylaxis of impairments in perception, concentration, cognitive processes, learning, and/or memory by the administration of a selective PDE9A inhibitor. Claim 3 limits the origin of the impairment (i.e. stroke or depression). Claim 7 limits the PDE9A inhibitor to 6-(cyclohexylmethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one.

"Prevention" or 'prophylaxis" is a potent claim that indicates that a drug will prevent a disease or symptom from occurring at any times regardless of the cause of the disease or symptom. The breadth of the claim is such that a PDE9A

inhibitor will prevent all impairments in perception, concentration, cognitive processes, learning, and/or memory, caused by any impairment;

b. *Nature of the invention*: The nature of the invention is a method of improving perception, concentration, cognitive processes, learning, and/or memory by increasing cGMP by the administration of a PDE9A inhibitor;

c. *The state of the prior art*: Cognitive processes, which include memory, learning, and perception, result from the integration of a complex network of cellular and molecular events. Weeber, et al. (Molecular Interventions, 2002), teach that "[t]he formation of memory, thus, depends upon the coordination of numerous cellular processes. A consequence of the complexity of memory formation however, is that disruption of one or a few of the molecular steps involved can be deleterious" (pg 378, col 1, paragraph 1, lines 1-4). Weeber, et al., summarize diverse cellular roles that affect human learning and memory in various diseases (Table 1).

cGMP plays an important role in the early stages of memory consolidation (Bernabeu, et al., NeuroReport, 1996, abstract). Phosphodiesterase, such as PDE5 and PDE9A, metabolize cGMP and inhibit cGMP-mediated pathways. Inhibitors of PDE5 and PDE9A prevent the PDE-mediated breakdown of cGMP, and intracellular cGMP levels within the cell rise as a consequence. Zaprinast is an effective inhibitor of both PDE5 (Reid, Current Pharmaceutical Design, 1999, abstract) and PDE9A (Phillips, US Patent No., 6,100,037, 2000, col 1, line 55). Zaprinast has been shown to increase the memory responses in treatment *in vivo* models of 7-nitroindazole-induced memory deficit (Pickaerts, et al., European

Journal of Pharmacology, 1997, abstract).

There is concern whether the cognitive improvements seen in rodents would translate to humans. Ebert and Kirch (European Journal of Clinical Investigation, 1998) teach that scopolamine, a drug commonly utilized to induce cognitive deficits, "cannot induce the full range of deficits seen in patients with Alzheimer's disease" (Abstract). Alzheimer's disease can reasonably be interpreted to be encompassed by impairment in cognitive processes.

d. *Level of one of ordinary skill in the art*: One of ordinary skill in the art would be scientists and clinicians who research and treat cognitive disorders;

e. *Level of predictability in the art*: While the murine models of cognition and learning are well-established, it is unclear just how these murine models relate to other organisms, especially humans. Ebert and Kirch question the appropriateness of basing therapies to improve cognitive function on scopolamine-induced impairment in mice and rats: "[S]colopamine cannot induce the full range of deficits seen in patients with Alzheimer's disease. Various aspects of memory are unaffected by scopolamine administration. The size of the memory deficits after scopolamine is much smaller than that seen in Alzheimer's disease" (pg 947, 2nd paragraph);

f. *Amount of direction provided by the inventor*: Applicant states that PDE9A inhibitors are effective for the treatment and prophylaxis of deficits of perception, concentration, cognitive processes, learning, and/or memory (instant specification, pg 4, lines 31-33). Applicant discloses that pyrazolopyrimidines are

PDE1, 2, and 5 inhibitors. It is noted that both PDE5 and PDE9A are selective for cGMP;

g. *Existence of working examples*: Applicant demonstrates the ability of PDE9A inhibitors to increase neuronal cGMP, *in vitro*, and improved memory in a social recognition test model in healthy rats; and,

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure*: For one of ordinary skill in the art to make and use the invention as described, an ordinarily skilled artisan would be required to first develop an animal model that adequately replicates cognitive deficits in which to test the selective PDE9A inhibitor. Next, the skilled artisan would have to translate the results from the specific animal model of cognitive deficits to treat a human or other animal that is not necessarily related to the model animal. Finally, the artisan would develop prophylaxis protocols, including pharmaceutical composition, dose, dosing schedule and route of administration. In doing so, the skilled artisan would overcome questions raised by Ebert and Kirch, who question whether scopolamine-induced (hence, drug-induced) cognitive impairment is an adequate model for cognitive deficits.

If unsuccessful in the first attempt, which is likely given the complexity of cognitive deficits, and the unpredictability of the art, one of ordinary skill in the art would be forced to determine whether: (A) the antagonist is effective, *in vivo*; (B) the model system provides adequate direction to prevent a cognitive deficit; (C) the translation from the animal model to treatment is appropriate; and, (D) whether the treatment protocol is sufficient. If unsuccessful again, which is likely

given the complexity of preventing cognitive deficits and lack of guidance from the instant specification and the prior art, one of skill in the art would have to repeat the entire, unpredictable process until successful.

Thus, it would require undue and unpredictable experimentation for one of ordinary skill in the art to make and use the claimed invention commensurate in scope with the rejected claims. Therefore, the claimed invention of a method preventing impairments in perception, concentration, cognitive processes, learning, and/or memory with PDE9A inhibitor.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over in Pickaerts, et al. (above), view of Andreevna, et al. (Journal of Neuroscience, 2001, provided in IDS), Phillips, et al (above).

15. Claim 1 is drawn to a method for improving perception, concentration, cognitive processes, learning, and/or memory comprising the administration of a selective PDE9A inhibitor. Claim 2 is drawn to a method of treating and/or prophylaxis of an impairment in perception, concentration, cognitive processes, learning, and/or memory comprising the administration of a selective PDE9A inhibitor. Claim 3 limits the cause of the impairment.

Pickaerts, et al., teaches that zaprinast enhances memory responses, *in vivo* (abstract). Phillips, et al., teach that PDE9 is inhibited by zaprinast (col 1, line 55). Both PDE5 and PDE9A utilize cGMP (as opposed to cAMP) as a substrate and belong to the same class of PDEs (Andreeva, et al., pg 9068, col 1, lines 9-15). Andreeva, et al., also teach that PDE9A is highly expressed in the brain (abstract) and that "the NO-cGMP signal transduction pathway is involved in memory formation in this task and that PDEs hydrolyzing cGMP, in particular PDE9A, which is expressed in the CA1 pyramidal neurons of the hippocampus, may participate as important determinants of intracellular cGMP concentrations" (pg 9075, col 1, lines 16-20). Given that (A) zaprinast enhances the memory response (Pickaerts, et al., above); (B) PDE9 is sensitive to zaprinast (Phillips, et al., above); and, (C) PDE9A is highly expressed in tissues associated with memory, it would have been *prima facie* obvious to one of ordinary skill in the art to administer a selective PDE9A inhibitors to improve or treat impairments of cognitive processes.

The specific PDE9A inhibitors claimed in Claims 6 and 7 appear free of the prior art.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1, 2, and 3 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 11, 9, and 10, respectively, of copending Application No. 10/524,956. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 11, 9, and 10, of the '956 application are drawn to a method of improving perception, concentration, cognitive processes, learning, and/or memory (Claim 11), treating or preventing an impairment thereof (Claim 9) or an impairment caused by various diseases (Claim 10)

comprising the administration a species of PDE9A inhibitors that are claimed as a genus in Claims 1-3 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 1, 2, and 3 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 11 and 12, respectively of copending Application No. 10/556,437. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 11 and 12 of the '437 application are drawn to a method of treating or preventing an impairment of perception, concentration, cognitive processes, learning, and/or memory thereof (Claim 11) or an impairment caused by various diseases (Claim 12) comprising the administration a species of PDE9A inhibitors that are claimed as a genus in Claims 1, 2, and 3 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 1, 2 and 3 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13 and 14, respectively of copending Application No. 10/556,224. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 13 and 14 of the '224 application are drawn to a method of treating or preventing an impairment of perception, concentration, cognitive processes, learning, and/or memory thereof (Claim 13) or an impairment caused by various diseases (Claim 14) comprising the

administration a species of PDE9A inhibitors that are claimed as a genus in Claims 1, 2 and 3 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 1, 2, and 3 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10, 8, and 9, respectively of copending Application No. 10/525,115. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 10, 8, and 9, of the '115 application are drawn to a method of improving perception, concentration, cognitive processes, learning, and/or memory (Claim 10), treating or preventing an impairment thereof (Claim 8) or an impairment caused by various diseases (Claim 9) comprising the administration a species of PDE9A inhibitors that are claimed as a genus in Claims 1-3 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL ZAREK whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, PATRICK NOLAN can be reached on (571) 272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4161